usually shows higher levels in obese patients. Leptin has proinflammatory effects and has been implicated in OA physiopathology.
Objective: To evaluate the relationship between body fat content with the amount of synovial fluid as a surrogate marker of inflammation and with levels of synovial fluid leptin in knee OA.
Methods: Patients aged 50 years or more with symptomatic osteoarthritis of the knee and joint effusion, Kellgren-Lawrence II-III. Demographics, disease duration and percentage of body fat (PBF) were assessed. Percentage of body fat was determined by bio-electrical impedance. Knee ultrasound (US) was performed evaluating and measuring the presence of effusion and at the suprapatellar midline. After US measurement joint aspiration was performed; all patients were evaluated approximately at the same time of the day. Synovial leptin levels were analyzed using a Human leptin ELISA kit (Biocompare, California, USA).
Results: Seventy consecutive female patients with symptomatic knee OA and Kellgren-Lawrence II-III were included, age 65 ±7.8 years, disease duration of symptoms 66 ±49.5 mo (12-200). Mean BFP was 42.34 ±5.11%. Patients were categorized into two groups based on BFP so that those with levels above the mean and median values (n= 36) were compared with the rest of the sample (n=34). Mean synovial fluid measurement was 9.59 ±2.79 mm. Mean level of leptin in synovial fluid was 76.76 ±38.66 ng/mL. Patients in the higher BFP group had similar amount of synovial effusion compared with those without such a high percentage (9.4 ±2.4 vs. 9.75 ±3.2 mm). However, patients with BFP above the mean and median values showed significantly higher synovial leptin levels than those with values below (88.47 ±46.8 vs. 60.24 ±19.5 ng/mL, p <0.005).
Conclusions: Higher synovial leptin levels were observed in patients with the highest body fat percentage as measured by bio-electrical impedance. On the other hand, synovial effusion did not appear to be linked to body fat content, indicating that body fat could be more related to metabolic abnormalities than to clinical signs of inflammation.

517
SYSTEMIC INFLAMMATION AND PAINFUL JOINT BURDEN IN OSTEOARTHRITIS: A MATTER OF SEX

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Purpose: Sex has a significant effect on osteoarthritis (OA) prevalence and severity, and women with OA often report greater pain than men with OA. Pain is the principal driver of health care use in this population. Importantly, there is a connection between pain and inflammation. While OA has not traditionally been considered a systemic joint disease, evidence suggests that systemic factors may play a contributing role in its pathogenesis and symptoms. The presence of multiple symptomatic joints among many with OA further suggests potentially underlying systemic mechanisms. Higher systemic concentrations of C-reactive protein (CRP) among OA populations compared to controls have been reported (CRP is a marker of inflammation), and a recent review suggested low-grade inflammation may play a greater role in symptoms than radiographic changes in OA. Sex differences in systemic inflammation may explain sex differences in OA symptoms. However, it may also be that for similar levels of inflammation, women report worse pain than men. In this study, we investigated the association between serum levels of CRP and the extent of painful joint involvement among individuals with end stage hip/knee OA, and whether the association differs between sexes.
Methods: Serum concentrations of CRP and cartilage oligomeric matrix protein (COMP- a proxy for disease burden) were determined by ELISA in 203 patients (115 females, 88 males) scheduled for total hip or knee replacement surgery for OA. Individuals reporting inflammatory arthritis were excluded. Patients completed a health questionnaire, and indicated on a homunculus all joints that were painful/problematic on most days for at least a month in the past 12 months. A count (not including the surgical joint) was developed (range: 0 to 21). Also elicited were age, sex, height and weight (used to calculate body mass index (BMI)), and comorbidities. Negative binomial regression was used to investigate the association between painful joint count (model outcome) and serum CRP concentrations, adjusting for age, sex, BMI, comorbidity count and serum COMP concentration. An interaction between sex and these biomarkers was tested. In a sensitivity analysis, all individuals reporting conditions associated with metabolic syndrome were excluded from analysis (high blood pressure, diabetes, heart disease and high cholesterol). For regression analyses, concentration values were log transformed.
Results: Mean age: 66 years among women (>96% were ≥50), 64 among men. Women had higher mean joint count (4.6 vs 2.5, p<0.001; 4+ joints reported by 42% women, 28% men). 51% of women were obese vs 36% in men (p=0.06). Median CRP concentration was higher in women (18.7 μg/ml vs 9.3, p=0.003). From adjusted analyses, the effects of both CRP and COMP were modified by sex (interaction terms: p<0.001 and =0.016, respectively). Increasing concentration of CRP was associated with greater painful joint burden among women, but not men (Count ratio (CR) of interaction term: 1.4 (95% CI: 1.2, 1.6); main effect: 0.9 (0.8, 1.0)). Results from the sensitivity analysis were consistent (CR of interaction: 1.5 (1.1, 1.9); main effect: 0.81 (0.6, 1.0).
Conclusions: This work suggests that there may be a dose-response association between painful joint burden in OA and systemic inflammation, and it appears the association is sex-specific. These findings create a potential opportunity to better risk-stratify women and men with OA pain, with a goal to tailoring assessment, treatment, and/or education strategies to optimize OA outcomes. In addition, given that high systemic concentration of CRP has been identified as a risk factor for diabetes and cardiovascular disease onset, these findings suggest that those with greater joint burden may be an OA subgroup at greater risk of comorbid disease onset, particularly women.

518
LOW-DOSE SOLUMATRIX MELOXICAM DEMONSTRATES LOW SYSTEMIC EXPOSURE AND EFFICACY IN PATIENTS WITH OSTEOARTHRITIS PAIN IN CLINICAL STUDIES

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Purpose: NSAIDs are frequently prescribed for the management of OA pain. Investigational, low-dose SoluMatrix® meloxicam, manufactured using SoluMatrix Fine Particle TechnologyTM, is being developed for management of osteoarthritis pain, providing lower systemic exposure than current commercially available meloxicam drug products to potentially minimize the risk of NSAID dose-related adverse events (AEs). Clinical studies have evaluated the pharmacokinetics (PK), efficacy, and safety of low-dose SoluMatrix meloxicam.
Methods: A phase 1 pharmacokinetic 4-period, 4-sequence crossover study in healthy adults aged 18 to 55 years evaluated the PK properties and safety of single doses of SoluMatrix meloxicam 5 mg (under fasted conditions), SoluMatrix meloxicam 10 mg (under fasted and fed conditions), and conventional meloxicam 15-mg tablets (Mobic®; Boehringer Ingelheim; under fasted conditions). Blood samples for PK assessment were collected pre-dose through 96 h post-dose. Separately, a phase 3 randomized, double-blind, placebo-controlled study enrolled adults ≥ 40 years of age with radiographically confirmed (Kellgren-Lawrence grade II-III) hip or knee OA. Eligible patients were chronic NSAID and/or acetaminophen users with a baseline WOMAC pain subscale score ≥ 40 mm (based on 100-mm Visual Analog Scale) and a documented OA pain flare (≥ 15-mm increase in WOMAC pain subscale score following washout of prior analgesics). Patients (N = 403) were randomized to receive once-daily treatment with SoluMatrix meloxicam 5 mg (n = 139), SoluMatrix meloxicam 10 mg (n = 130), or placebo (n = 134). The primary efficacy parameter was the mean change from baseline in WOMAC pain subscale score at week 12.
Results: In the PK study, 28 participants were enrolled and 25 participants completed the study. SoluMatrix meloxicam 10 mg attained similar mean peak plasma meloxicam levels ± SD compared with conventional meloxicam 15-mg tablets (1.25 ± 0.25 μg/mL vs 1.29 ± 0.42 μg/mL, respectively; under fasted conditions; Table). Both SoluMatrix meloxicam 5 mg and 10 mg achieved a more rapid median time to peak plasma meloxicam levels under fasted conditions than conventional

meloxicam 15-mg tablets (2.0 vs 4.0 h, respectively). SoluMatrix meloxicam 10 mg demonstrated approximately 33% lower overall systemic exposure compared with conventional meloxicam 15-mg tablets. As described for other NSAIDs, food decreased the rate but not the overall extent of SoluMatrix meloxicam absorption (Table). Treatment-related AEs included 1 case each of mild abdominal pain and mild diarrhea in the SoluMatrix meloxicam 10 mg (fed) group and 1 report of mild somnolence in the SoluMatrix meloxicam 5 mg group. In the separate phase 3 study in patients with OA pain, 350 (86.8%) of 403 patients completed the 12-week study. SoluMatrix meloxicam 5 mg (mean [standard error] (SE) -36.5 [2.49]; P = 0.0005) and 10 mg (-34.4 [2.68]; P = 0.0059; Table) provided significantly greater pain relief as measured by the primary efficacy parameter compared with placebo (-25.68 [2.64]). Patients in the SoluMatrix meloxicam 5 mg (P = 0.0049) and 10 mg (P = 0.0012) groups reported significant differences in the distribution of responses in the patient global impression of change (from baseline) compared with placebo. Patients in the SoluMatrix meloxicam 5 mg and 10 mg groups demonstrated a numerically greater mean percentage reduction in pain (by NPRS) at 2 h (-33.44% for the 5 mg group; P = 0.0294 and -30.54% for the 10 mg group; P = 0.1357) compared with placebo (-24.32%). Low-dose SoluMatrix meloxicam 10-mg (mean ± SE: 48.4 ± 7.13 doses; P = 0.0013) and 5-mg (52.4 ± 6.61 doses; P = 0.006) treated patients required significantly fewer rescue medication doses over 12 weeks compared with placebo (73.2 ± 7.03 doses). Across SoluMatrix meloxicam groups, the most common AEs (occurring in ≥ 2% of patients) were diarrhea, headache, OA, and urinary tract infection. No deaths or serious AEs were reported.

Table. Summary of Plasma Pharmacokinetic Parameters

Parameter	SoluMatrix Meloxicam 5 mg (Fasted)	SoluMatrix Meloxicam 10 mg (Fasted)	Conventional Meloxicam Tablets 15 mg (Fasted)	SoluMatrix Meloxicam 10 mg (Fed)
T_{max} (h), median (min–max)	2.0 (0.5–4.1)	2.0 (1.0–5.0)	4.0 (2.0–8.0)	5.0 (1.5–16.0)
C_{max} (µg/mL), mean ± SD	0.64 ± 0.14	1.25 ± 0.25	1.29 ± 0.42	0.97 ± 0.17
$AUC_{0\text{-}inf}$ (µg·h/mL), mean ± SD	13.6 ± 3.3	29.2 ± 11.0	40.9 ± 11.7	27.1 ± 11.5
$t_{½}$ (h), mean ± SD	22.3 ± 10.9	22.0 ± 10.1	23.6 ± 10.0	22.3 ± 9.9
Lambda z (1/h), mean ±SD	0.036 ± 0.013	0.036 ± 0.012	0.034 ± 0.012	0.036 ± 0.013

$AUC_{0\text{-}inf}$, area under the concentration-time curve from time 0 extrapolated to infinity; C_{max}, peak plasma concentration; lambda z, terminal elimination rate constant; $t_{1/2}$, apparent terminal elimination half-life; T_{max}, time to peak plasma concentration.

Conclusions: Low-dose SoluMatrix meloxicam 5 and 10 mg, under fasted conditions, provided comparable peak plasma levels, but with an earlier time to peak plasma levels and with a 33% lower overall systemic exposure compared with conventional meloxicam 15-mg tablets. SoluMatrix meloxicam 5 and 10 mg once daily provided significantly greater relief from OA pain compared with placebo. These data suggest that low-dose SoluMatrix meloxicam is a potentially promising treatment option for adults with OA pain.

519
DIFFERENCE IN BODY COMPOSITION BETWEEN PATIENTS WITH EARLY KNEE OSTEOARTRHRITIS COMPARED WITH LATE KNEE OA IN A MEXICAN POPULATION

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Purpose: Introduction. Osteoarthritis (OA) is a chronic and degenerative condition. It affects not only cartilage but also bone, synovial and periarticular soft tissue. Obesity is a recognized risk factor for knee OA and weight loss reduces the risk of OA progression. Some studies have examined the relationship between other components of body composition (BC), such as muscle mass and the risk of OA. Although several studies have failed to determine a significant relationship between fat distribution and the risk of knee OA. We did not found studies that it examined differences in body composition between early and late OA. If there are difference, it could be part of the preoperative treatment before undergo to total knee arthroplasty.

Objective: To describe difference in BC between patients with early and late knee OA in a Mexican population.

Methods: Patients and methods. The study was performed in a tertiary hospital care. The patients in the early OA (EOA) had the following inclusion criteria: patients with knee OA criteria according to American College of Rheumatology, younger than 55 years old, a Kellgren-Lawrence score less than or equal to 2 on the knee X-ray and without previous surgery in the studied knee; Patients with late OA (LOA) group had the following inclusion criteria: evaluation in the outpatients clinic of joint surgery department, with a proposal of a primary joint replacement surgery due to pain and/or disability due to knee OA, Kellgren-Lawrence III or IV score on knee X-ray. Exclusion criteria in EOA and LOA: patients with autoimmune inflammatory joint disease, traumatic or congenital lesions. Clinimetric evaluation. All patients had an interview to collect epidemiological data, joint function with WOMAC knee index; All patients were evaluated using bioelectrical impedance analysis in order to collect BC with multifrequency bioimpedance (InBody 720®). Analysis. We used a descriptive and bivariate analysis using appropriate to compare median between EOA vs. LOA.

Results: Results. 110 patients were evaluated, 56 with EOA and 54 LOA. The EAO group were younger than LOA patients: median 48.5 vs. 65.5 years old (p =0.001). The women proportion was superior in both groups: 71.8 women vs. 28.2 men. The EOA had a median of 11 education years vs. 7 in LOA (p= 0.03). The OA evolution was 20.3 months in EOA vs. 60 months in LOA (p=0.001).

In table 1 we describe the BC in EOA vs. LOA The differences that we found were only in female gender. In LOA group women had less total lean mass, lean mass index and fatter mass index than EOA group. We also found that women in LOA had less lean mass in the extremity affected by OA compared to EOA group. We did not find differences between men gender groups. (Table 2).

Conclusions: Conclusions. The female patients with LOA in the knee had more problems with the body compositions compared with the female with EOA. The men groups (EOA vs. LOA) did not have differences. The lean mass is lower en female patient with LOA compared with EAO. Probably It is one of the first study that evaluate leg affected composition between EOA vs. LOA; it finding could have preoperative treatment implications.

Table 1- Body composition between Early OA (EOA) vs. Late OA (LOA)

Variable		EAO n= 56	LOA n=54	p value
Body mass index (kg/m2)*				
	Women	29.8 (22.2-45.6)	30.4 (20.2-42.9)	0.43
	Men	28.3 (24.3-40.1)	29.3 (23.1-38)	0.58
Total lean mass (kg)*				
	Women	25 (18-36)	20.8 (13.4-26.6)	0.001
	Men	27.6 (19-38.5)	27.9 (21.5-41.3)	0.71
Lean mass Index (kg/m2)*				
	Women	9.9 (8.1-12.8)	8.8 (7.1-10.8)	0.001
	Men	10.2 (8.4-13.3)	10.1 (8.5-12.6)	0.71
Fat mass (kg)*				
	Women	28.4 (14-60)	32.5 (14.4-52.2)	0.14
	Men	26 (13-48)	27.1 (13.8-45.3)	0.71
Fatter mass index (Kg/m2)*				
	Women	11.2 (4.7-24.3)	14.2 (6.2-23.4)	0.005
	Men	10.2 (5-17.8)	10.2 (5.7-16.8)	0.71

*median (range)

Table 2. Affected leg composition and EOA vs. LOA

Variable		EOA	LOA	p value
Total lean mass in affected right leg (kg)				
	Women	6.57 (4.84-9.81)	5.1 (2.44-7.63)	0.009
	Men	7.28 (5.31-8.64)	7.65 (6.08-10.76)	0.508
Total lean mass in affected left leg (kg)				
	Women	6.44 (4.59-8.75)	5.12 (4.07-7.12)	0.008
	Men	7.39 (6.95-10.41)	7.45 (5.77-8.33)	0.819